



Recovery of low plasma BDNF over the course of treatment among patients with bulimia nervosa

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ABSTRACT

Recent studies have suggested that brain-derived neurotrophic factor (BDNF) is associated with energy balance, eating behaviors, and psychological states such as depression. Although decreased BDNF levels in patients with bulimia nervosa (BN) have been reported, the mechanism is still unclear. Few studies have investigated longitudinal changes of BDNF in BN patients. We investigated changes in the levels of plasma BDNF before and after inpatient treatment. Subjects were 16 female patients with BN and 10 control females. The levels of plasma BDNF were measured. In seven patients who completed a 4-week inpatient treatment program based on cognitive behavior therapy, levels of plasma BDNF were measured twice, before and after inpatient treatment. Plasma BDNF levels were significantly lower in BN subjects than in controls. BDNF levels were significantly higher following inpatient treatment. Increased plasma BDNF after inpatient treatment suggests that lower plasma BDNF levels in BN patients are associated with abnormal eating behaviors, especially binge eating.

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1. Introduction

Bulimia nervosa (BN) is a chronic, frequently treatment-resistant disorder, characterized by specific symptoms such as prominent body image distortion, a morbid fear of fatness, binge eating, consequent compensatory behaviors including subsequent self-induced vomiting or laxative abuse, excessive exercising, and self-starvation (American Psychiatric Association, 1994). It remains to be clarified whether characteristic psychological features such as anxiety, depressive symptoms and morbid body image distortion are primary causes or just the result of abnormal eating behaviors.

Brain-derived neurotrophic factor (BDNF) is a member of the family of neurotrophins, which includes nerve growth factor (NGF), neurotrophin-3 (NT-3), NT 4/5, NT-6 and NT-7 (Chaladakov, 2011; Noble et al., 2011).

BDNF plays an important role in the growth and maintenance of several neuronal systems, serves as a neurotransmitter modulator, and participates in use-dependent plasticity mechanisms, such as learning and memory (Noble et al., 2011). BDNF is widely distributed in the central nervous system, beginning early in development and extending throughout the lifetime. In addition, BDNF and its tyrosine kinase receptor, TrkB, are expressed in various hypothalamic nuclei associated with eating behavior (Kernie et al., 2000). Some authors have demonstrated that hypothalamic BDNF may be an important signaling effector that controls glucose, energy balance and eating behavior (Xu et al., 2003); hence, BDNF, like NGF, is considered not

only neurotrophic, but also a metabotropic factor (Chaladakov, 2011). In the same vein, BDNF knockout mice develop obesity and hyperphagia (Kernie et al., 2000; Rios et al., 2001; Fox and Byerly, 2004). The infusion of BDNF into the central nervous system induced weight loss, and direct infusion into the hypothalamus decreased feeding (Rios et al., 2001). In addition, in genetically obese, insulin- or leptin-resistant animal models, the peripheral injection of BDNF decreased weight and appetite as well as improved glucose, cholesterol, and nonesterified free fatty acid levels (Tonra et al., 1999; Ono et al., 2000; Nakagawa et al., 2003; Xu et al., 2003). These results suggest that BDNF is associated with appetite, eating behavior, and conditions linked to cardiometabolic dysfunction, e.g., atherosclerosis, obesity, type 2 diabetes, and metabolic syndrome in humans (Chaladakov et al., 2004).

However, anorexic patients consistently showed lower blood BDNF levels (Nakazato et al., 2003; Monteleone et al., 2004, 2005; Nakazato et al., 2009; Saito et al., 2009). In addition, genetic studies have reported significant and consistent associations of BDNF variants with eating disorder patients (Ribases et al., 2003; Gratacos et al., 2007). Normal-weight bulimic patients also showed lower blood BDNF (Nakazato et al., 2003; Monteleone et al., 2005); however, the results were relatively inconsistent compared with anorexic patients. In depressive patients, previous studies consistently reported significantly reduced blood BDNF levels, which were normalized with antidepressant therapy (Shimizu et al., 2003; Huang et al., 2008; Piccinni et al., 2008). Also, depressive symptoms are common among BN patients (Garfinkel et al., 1980). Thus, the improvement of depressive symptoms could induce the recovery of low BDNF levels even among BN patients.

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In the present study, we measured levels of plasma BDNF among BN patients to assess the relationship with psychological symptoms such as depression, anxiety and eating disorder symptoms, employing cross-sectional and longitudinal analyses. We hypothesized that lower plasma BDNF levels would recover to the levels of controls based on the improvement of abnormal eating behaviors as well as psychological symptoms including depression, anxiety, and eating disorder.

2. Methods

2.1. Subjects

The subjects consisted of 16 females with BN and 10 female controls. All the BN subjects were recruited from the outpatient clinic. They were interviewed using the H Section of the Structured Clinical Interview for DSM-IV (SCID) (Takahashi et al., 2003), and all met DSM-IV criteria (American Psychiatric Association, 1994) for BN and the binge eating/purging type. The controls were healthy age-matched women. The controls completed the SCID screening module and the first two questions of the SCID regarding lifetime major depressive episodes; they were found to have no history of physical or psychiatric disorders. None of the participants had taken any medication before entering this study. Inpatient treatment was carried out in an open general psychiatry unit on a voluntary basis, using a 4-week behavioral program along with some cognitive treatment. Patients who had major depressive disorder were excluded from this program. None of the participants received any psychopharmacological medication through the inpatients treatment. All subjects provided written informed consent to participate in the study. This study was approved by the institutional review committee of Osaka City University Graduate School of Medicine.

2.2. Procedures

Following an overnight fast, blood samples were taken between 8 and 10 a.m. with 0.5 ml of heparin. To evaluate the basic nutritional state, blood cell counts, total protein, cholesterol, and blood sugar were measured. None of the participants had liver or renal dysfunction, or demonstrated signs of inflammation. There was no other clinical and laboratory evidence of medical illness in any participant. The heparinized blood sample was centrifuged (1000×g, 10 min, at 4°), and supernatant (plasma) was maintained at –70° until the assay. The plasma levels of BDNF were measured with enzyme-linked immunosorbent assay (ELISA) kits (Quantikine, R & D Systems, Minneapolis, MN, USA). Measurements were carried out according to the manufacturer's instructions. All samples were examined in duplicate. The sensitivities of BDNF tests were 20 pg/ml. Intra-assay and interassay coefficients of variations were less than 4.7%.

All participants filled out the Eating Disorder Inventory (EDI) (Garner et al., 1983), Beck Depression Inventory (BDI) (Beck et al., 1961), and State-Trait Anxiety Scale (STAI) (Spielberger et al., 1970) on the day of examination.

2.3. Statistical analyses

Nonparametric analyses were mainly used because the number of subjects, particularly at follow-up, was small. The Mann-Whitney *U* test between BN and controls, the Spearman correlation coefficient between BDNF and psychological and nutritional states, and the Wilcoxon signed rank test (between pre- and post-inpatient treatment) were used. *P*-values <0.05 were considered significant. All statistical analyses were performed using SPSS 11.5 for Windows (Chicago, IL, USA).

3. Results

There were no significant differences in the age and body mass index (BMI) between the BN subjects and controls (Table 1). None of the BN patients who participated in this study had past histories of substance abuse and sexual/physical abuse. Five patients had a history of anorexia nervosa (AN) and the duration after recovery from AN was 1, 4, 4, 6 and 8 years, respectively.

The mean age at onset of BN was 19.5 years (standard deviation (S.D.): 4.9). Mean frequencies of binge-eating, vomiting, and laxative use per week in the participants with BN were 8.9 (S.D.: 10.1), 7.9 (S.D.: 7.2), and 4.3 tablets (S.D.: 15.0), respectively. The EDI subscale scores, BDI, STAI-state and STAI-trait scores were significantly higher in the BN subjects than in the controls. There were no significant differences in the white blood cell count, red blood cell count, total protein level, cholesterol or blood sugar level, and cortisol level between the BN subjects and controls. BN subjects showed significantly lower BDNF levels than the controls.

Table 1
Demographics and BDNF levels in subjects with bulimia nervosa and controls.

N	Bulimia nervosa	Controls	Mann-Whitney
	16	10	<i>U</i> (<i>p</i>)
Age (years)	25.3 ± 5.3 ^a	27.8 ± 2.0	56 (0.22)
Body mass index	19.6 ± 3.2	21.0 ± 2.2	49 (0.11)
Lowest body mass index	16.9 (2.3)	N.A.	N.A.
Eating Disorder Inventory			
Drive for thinness	15.0 ± 4.3	2.5 ± 4.2	6 (<0.001)
Bulimia	11.9 ± 5.0	0.4 ± 0.7	0.5 (<0.001)
Body dissatisfaction	15.7 ± 5.4	8.3 ± 5.6	31 (0.01)
Ineffectiveness	15.3 ± 5.4	1.7 ± 1.5	0.5 (<0.001)
Perfectionism	6.1 ± 2.9	1.9 ± 1.8	15 (<0.001)
Interpersonal distrust	7.3 ± 3.6	1.7 ± 2.5	12 (<0.001)
Interceptive awareness	17.3 ± 6.8	1.2 ± 3.1	2 (<0.001)
Maturity fears	8.2 ± 4.3	3.2 ± 2.3	22 (0.006)
BDI	23.5 ± 8.4	2.4 ± 3.4	1.5 (<0.001)
STAI-state	56.6 ± 10.2	34.9 ± 7.4	5.5 (<0.001)
STAI-trait	62.7 ± 7.5	38.1 ± 5.1	0 (<0.001)
White blood cell (/μl)	5200 ± 1695	5670 ± 1869	65 (0.57)
Total protein (g/dl)	7.9 ± 2.3 ^b	7.6 ± 0.4	55 (0.77)
Cholesterol (mg/dl)	189 ± 25 ^c	190 ± 37	53 (0.86)
Blood sugar (mg/dl)	82 ± 25 ^d	84 ± 6.8	43 (0.17)
Cortisol (μg/dl)	15.0 ± 7.1 ^b	10.1 ± 5.4	34 (0.08)
BDNF (ng/ml)	1.89 ± 1.67	6.57 ± 6.09	37 (0.02)

^aValue (S.D.), patients have missing value (^b*n* = 12, ^c*n* = 11, ^d*n* = 13).

BDI: Beck Depression Inventory, STAI: State-Trait Anxiety Scale; BDNF: brain-derived neurotrophic factor.

The correlations between BDNF and background parameters were examined in all participants, and only in patients with BN; however, there were no significant correlations in any pairs.

In seven BN patients, levels of BDNF were measured twice, before and after inpatient treatment (Table 2). There were no significant differences in the background parameters, psychological variables, or levels of BDNF between those entered for inpatient treatment and the other outpatients. Frequencies of binge eating, self-induced vomiting, and laxative use per week significantly reduced after inpatient treatment. There were no significant changes of the EDI subscale scores, except for drive for thinness. There were no significant changes of BDI, STAI-state and STAI-trait scores after inpatient treatment. As shown in Table 2 and Fig. 1, the level of BDNF was significantly increased after inpatient treatment (effect size on Wilcoxon signed-rank test was large, at 0.85), although there were no significant changes in the complete blood tests and cortisol level between pre- and post-inpatient treatment.

4. Discussion

To our best knowledge, this is the first study to report that low plasma levels of BDNF in BN patients recovered to the level of controls when binge eating and vomiting were stopped, even though the general psychopathology did not fully recover. The reasons for this could include the following:

The first possibility is that improvement of the psychological state influenced the level of BDNF in the current study. It has been reported that serum BDNF levels in patients with major depression were significantly reduced, and that taking selective serotonin reuptake inhibitors (SSRI) induced BDNF level recovery (Karege et al., 2002; Shimizu et al., 2003; Piccinni et al., 2008). It has also been reported that BDNF-conditional mutant mice were hyperactive after exposure to stressors (Rios et al., 2001). In addition, scale scores regarding eating disorder were significantly associated with serum levels of BDNF in some studies (Nakazato et al., 2006; Mercader et al., 2010). These findings suggested the possibility that BDNF plays an essential role in the regulation of depression and anxiety, as well as in food intake behavior. It is well known that depressive symptoms exhibit a high degree of comorbidity

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